UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/780,507	02/17/2004	James I. Mullins	08987-023001	7871

26161 7590 02/07/2007

FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
PENG, BO	
ART UNIT	PAPER NUMBER
1648	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
30 DAYS	02/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/780,507	MULLINS ET AL.	
	Examiner	Art Unit	
	Bo Peng	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/13/07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-62* is/are pending in the application.

4a) Of the above claim(s) *1-14,16-18,31-44 and 52-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,19-22,25-30 and 45-51* is/are rejected.

7)☒ Claim(s) *15,48 and 51* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/8/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Restriction election

1. The Office acknowledges the receipt of Applicant's restriction election, filed on November 13, 2006. Applicant elects Group VI, Claims 15-30 and 45-51, without traverse. Applicants elect SEQ ID NO: 25. The requirement is made FINAL.

2. Accordingly, Claims 1-62 are pending. Claims 1-14, 16, 17, 18, 31-44, and 52-62 are withdrawn as non-elected. Claims 15, 19-22, 25-30 and 45-51 are under consideration in this Office action.

Information Disclosure Statement

3. The information disclosure statement submitted on January 17, 2007 is in compliance with the provisions of 37 CRF 1.97. Accordingly, the information disclosure statement has been considered by the examiner. An initialed and dated copy of Applicant's IDS form 1449 is attached to the instant Office action.

Claim Objections

4. Claims 15, 48 and 51 are objected to because of the following informalities: "an ancestor" or "a COT protein" should be "the Ancestor" or "the COT protein" because it refers to specific types of proteins. Claim 48 should refer the LScot or MMcot sequence to specific SEQ ID NO: rather than to Figures. Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 45-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 45 and 49 are indefinite. The terms "a highly diverse" "widely dispersed..., geographically-restricted..." are relative terms. The specification does not provide a standard for ascertaining the requisite degree or reference frame, which would allow one of ordinary skill in the art to be reasonably appraised of the scope of the invention. This rejection affects all dependent claims.

8. The term "a circulating variant" renders Claims 45 and 48 indefinite because it is not explicitly defined in the claims nor the specification. According to the specification: "The term 'circulating virus' refers to virus found in an infected individual" (Paragraph [0078]). However, The term of "circulating" is relative to a time frame, and the term of "a variant" is relative to a reference sequence. Without appropriate the definition for a time frame or reference viruses, one of skill would not know what "a circulating variant" is. For example, "a circulating virus" in the same HIV-infected patient could be totally different at different time points depending on the drug treatment and the stages of disease progression. Also, given the quasispecies and plastic nature of HIV, a circulating HIV variant yesterday may not be a circulating variant today. Thus, the specification does not provide a standard for ascertaining the requisite reference frame, which would allow one of ordinary skill in the art to be reasonably appraised of the metes and bounds of the invention.

9. Appropriate corrections are required.

Claim Rejections - 35 USC § 112, first paragraph

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 15, 19-22, 25-30 and 45-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

> *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detail chemical structure of the encompassed genus of undefined nucleotide fragment, proteins or polypeptides. Therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Lid.*, 18 USPQ2d 1016.
>
> Applicant has disclosed a limited number of species; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception in either case cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequences themselves are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).
>
> A description of a genus of protein sequences may be achieved by means of a recitation of a representative number of polypeptide sequences, defined by amino

> acid sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

12. Claims 15, 19-22, 25-30 and 45-51 are drawn to an isolated expression construct/a vector/an cultured prokaryotic or eukaryotic cell comprising the following operably linked elements: a transcriptional promoter; a nucleic acid encoding an ancestor or COT protein; and a transcriptional terminator, wherein the transcriptional promoter is a heterologous promoter, wherein the promoter is a cytomegalovirus promoter, wherein the eukaryotic cell is a mammalian cell, wherein the eukaryotic cell is an *S. cerevisiae* cell, wherein eukaryotic cell of Claim 21, which is a human cell, wherein the prokaryotic cell is an *E. coli* cell (Claims 15, 19-22, and 25-30); An isolated COT viral gene sequence, and fragments thereof, wherein the sequence is a determined sequence of a highly diverse viral strain, subtype or group, wherein the COT viral gene sequence is an HIV-1 viral gene sequence, an HIV-2 viral gene sequence, or a Hepatitis C viral gene sequence, wherein the COT viral gene sequence is of HIV-1 subtype A, B, C, D, E, F, G, H, J, AG, or AGI; HIV-1 Group M, N, or O; or HIV-2 subtype A or B, wherein the COT viral sequence has at least 70% identity with an LScot or MMcot sequence set forth in FIGS. 9 to 17 or 27 to 35, and wherein the sequence does not have 100% identity with any circulating variant, wherein the COT viral gene sequence is of widely dispersed HIV-1 variants, geographically-restricted HIV-1 variants, widely dispersed HIV-2 variants, or geographically-restricted HIV-2 variants, wherein the COT viral gene sequence is an env gene or a gag gene, wherein the sequence encodes a COT protein (Claims 45-51).

13. First of all, according to "Guidelines for Examination of patent Application under 35 U.S.C. 112, first paragraph, 'Written Description' Requirement" 66 F. R. 1099, 1150: "The

claimed invention as a whole may not be adequately described if the claims require an essential or critical feature that is not described in the specification and is not conventional in the art or to known one of skill in the art" (Jan 5, 2001, left column, first paragraph). The instant claims lack written description because the essential feature of the claimed COT sequence is not described. According to specification, a "COT sequence" is a position at a node or on a branch of a phylogenetic tree having completely specified branch lengths, and determined through application of a COT Least Squares Method or a COT Minimum of Means Method (Paragraph [0077]). A phylogenetic tree is a tree showing the evolutionary interrelationships among various species or other entities that are believed to have a common ancestor. Since a phylogenetic tree could be constructed among any entities believed to have a common ancestor, the entities of the tree could be selected from within a species, across species or across genera within any time frame. In the instant case, to determine the COT sequence, the specific sequence reference frame that defines the entity of a phylogenetic tree is an essential and necessary factor. However, the claimed COT sequence is not adequately described since the reference frame/entity is lacking or not defined. Without a reference frame/entity, the COT sequence is unknown because, without specific sequence data to which the algorithm is to be applied, the resulting calculated COT sequence is not known. Since the COT sequence is not conventional in the art or known to one of ordinary skill in the art, and a phylogenetic tree could be constructed among any entities, one of ordinary skill in the art cannot envision what the COT sequence is, even when accompanied by a method of obtaining the claimed sequence. Therefore, the claimed COT sequence does not have sufficient characteristic for written description.

14. Secondly, because the specification does not define the entities of phylogenic trees for the

COT sequence, and there is no structural limitation to the COT protein (Claim 15), "an isolated COT viral sequence, and fragments thereof" (Claim 45), the scope of the claims encompasses any sequences under the Sun. The possible variations are infinite to such so-called COT sequences. The MPEP states that written description for a genus can be achieved by a representative number of species within a broad genus. Here, while having written description of a few specific COT sequences of HIV gag, env or other viral genes identified in the specification tables and/or examples, the specification lacks sufficient variety of species to reflect this variation in the genus, therefore, lacks a representative number of species of such broad genus of the COT sequences.

15. Since the claims lack sufficient structural and functional characteristics of the COT sequences and the specification lacks sufficient variety of species to reflect this highly variable genus of any COT sequences, there is no indication that Applicant was in possession of all isolated expression construct/a vector/a cultured prokaryotic or eukaryotic cell comprising a nucleic acid encoding the COT protein as broadly claimed.

Claim Rejections - 35 USC § 112 –Scope of Enablement

16. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 15, 19-22, 25-30 and 45-51 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling to make the specific HIV COT

sequence SEQ ID NO:X, such as SEQ ID NO:25, does not reasonably provide enablement to make any other COT sequences, and does not reasonably provide enablement to use the COT sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth.

"[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Genentech Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (BdPatAppInt 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

18. First, as discussed above, the scope of Claims 15, 19-22, 25-30 and 45-51 encompasses an infinite number of the COT sequence. It would require a considerable experimentation for one of skill in the art to make and test these COT sequences.

19. Secondly, the specification provides little guidance regarding how to use the COT sequence. The specification refers to application of the COT sequence for prophylactic and diagnostic use (Abstract). However, the specification does not teach how to use the COT sequence for any specific diagnostic application. Moreover, in general, most proteins, such as host proteins, are not suitable for use as vaccines.

20. Furthermore, although there is some discussion about the rationale to use the COT sequence as an HIV vaccine, the specification has not disclosed any real data, *in vitro* or *in vivo,* to show that the COT sequence could be an effective vaccine. Up to now, HIV vaccines have not proved to be effective for the intended purpose due to the well-known difficulties inherent to development of HIV vaccines. Some of those problems are outlined here: 1) the extensive genomic diversity associated with the HIV retrovirus, due in large part to error prone reverse transcription of its single-stranded RNA genome; 2) the existence of latent forms of the virus; 3) the ability of the virus to "immune escape" from natural and adoptive immunity against the virus; 4) the modes of viral transmission, including both cell-to-cell and free virus transmission; 5) the complexity and variation of the elaboration of the disease and; and 6) the property of some portions of HIV proteins or peptides to actually cause immunosuppression or other detrimental consequences. The existence of these obstacles prevents one of ordinary skill in the art from recognizing that current HIV vaccines are effective. "The inability to solve fundamental scientific questions is the root cause for why a successful vaccine is not currently with our grasp"

(Desrosiers RC. Nature Medicine Vol. 10 (2004), pp. 221-223). To date, several clinical trials have been conducted but in every situation, the immunogen failed to induce protective immunity, failed to control viremia, and failed to protect individuals at a high risk from infection. Moreover, no experimental vaccine candidates so far have been proven to be effective to protect monkeys from SIV infection in animal models.

21. The existence of these obstacles also prevents one of ordinary skill in the art from accepting any alleged vaccine regimen, including the COT sequence, on its face value. In order to provide proof of utility with regard to drugs and their uses, either clinical or *in vivo* or *in vitro* data, or a combination of these can be used. However, the data must be such as to convince one of ordinary skill in the art that the proposed utility is sufficiently established. See in re Irons, 340 F. 2d 924,144 USPQ 351 (CCPA 1965), Ex parte Krepelka, 231 USPQ 746 (PTO Bd. Pat. App & Inter.1986) and Ex pane Chwang, 231 USPQ 751 (PTO Bd. Pat. App & Inter. 1986). In the instant case, the rationale to use the COT sequence as a HIV vaccine, without specific scientific data presented in the specification, is insufficient to convince one of ordinary skill in the art that the claimed COT sequences can be effective for their intended use.

22. Since the COT sequence is not conventional in the art or known to one of ordinary skill in the art, one of ordinary skill in the art is unable to fully predict possible functions and applications of the COT sequences based on the teaching of the instant specification, therefore, clearly would not know how to use the claimed COT sequence.

23. Although the specification teaches how to make a specific HIV COT sequence SEQ ID NO:25, it does not teach how to make any other COT sequences, and how to use the COT sequence. Since the scope of Claims 15, 19-22, 25-30 and 45-51 encompasses an infinite number

of the COT sequence, in view of the unknown nature of the COT sequence, and lack of guidance and working examples in the specification. it would require undue experimentation for one of skill in the art to make an infinite number of the COT sequence, and to find the use for the COT sequence. Therefore, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim Rejections - 35 USC § 102

24. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

25. Claims 15, 19-22, 25-30 and 45-51 are rejected under 35 U.S.C. 102(b) as being anticipated by Shiver (WO 98/34640; Note: The sequence alignment is based on the SEQ ID NO: 1 in 09/017,981, which is the national stage of WO 98/34640).

26. Claims 15, 19-22, 25-30 and 45-51 are summarized in Paragraph 12.

27. Shiver (WO 98/34640) teaches a codon-optimized HIVgag sequence (SEQ ID NO:1) (p. 29, 30 and Claim 4). The codon-optimized HIVgag gene SEQ ID NO:1 is a viral sequence originated from HIV-1 serotype B, HIV_{IIIB} or CAM-1 strain (p. 15). The codon-optimized HIVgag gene SEQ ID NO:1 has 74.9% identity with LScot (SEQ ID NO: 24), and 74% identity to MMcot (SEQ ID NO: 26) (see attached sequence alignment), and does not have 100% identity with any circulating variant. Thus, Shiver's codon-optimized HIVgag gene meets very limitation

of Claims 45-51. Shiver also teaches an expression vector, designated V1Jns-FLgag, which expresses codon-optimized gag gene (see Example 1 and 2, p.24-26). The vaccine plasmid backbone contains the CMV immediate-early (IE) promoter and intron A, a bovine growth hormone-derived polyadenylation and transcription termination sequence as the gene expression regulatory elements, and a minimal pUC backbone. The pUC sequence permits high levels of plasmid production in *E. coli*. Shiver shows the expression of gag protein in 293 cells (Figure 1).

28. As shown above, Shiver's codon-optimized HIVgag gene SEQ ID NO:1 meets every limitation of Claims 45-51. Moreover, since the COT sequence could be any sequence as discussed in Paragraph 15, Shiver's expression construct/cells/vectors comprising the codon-optimized HIVgag sequence also meets all features of Claims 15, 19-22 and 25-30. Therefore, the instant Claims 15, 19-22, 25-30 and 45-51 are anticipated by Shiver.

29. It is noted that Applicant has elected SEQ ID NO:25 as the COT sequence for examination. Please note that the COT sequence SEQ ID NO: 25 of Claims 45-51 is interpreted as a variant of HIVgag gene encoding a gag protein for following reasons: The claims are drawn to a product, not a method of making a product. Product-by-process claims are not limited to the manipulation of the recited steps, only the structure implied by the steps (MPEP 2113). "The patentability of a product does not depend on its method of production". In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985) See MPEP 2113. Here, given the fact that the protein encoded by the COT sequence SEQ ID NO: 25 has more than 99.4% identity to Shiver's HIVgag protein (see attached amino acid sequence alignment), the COT viral sequence SEQ ID NO: 25 appears to be a HIVgag variant rather than a different product. Thus, the COT sequence ID NO:25 is interpreted as a HIV gag variant.

Remarks

30. No claims are allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, Ph.D. can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Bo Peng, Ph.D.
January 31, 2007

SHANON FOLEY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600